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TNO report

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Sleep and Alertness management IV: Effects of alertness enhancers caffeine and modafinil on performance in marmosets

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Slaap- en Alertheidsmanagement IV: Effect van de alertheidsverhogende middelen caffeïne en modafinil op taakverrichting in marmosets

Probleemstelling

In opdracht van het Ministerie van Defensie wordt door TNO Defensie en Veiligheid onderzoek gedaan naar praktische richtlijnen om tijdens militaire missies ernstige vermoeidheid te voorkomen en de prestaties en alertheid te optimaliseren. Ervaringen met militaire missies hebben namelijk geleerd dat de nadelige effecten van slaaptekort een zeer belangrijke rol speelden bij de uitvoering van de missies. Aangezien militaire missies zich niet tussen negen en vijf uur afspelen maar er ook 's nachts prestaties geleverd moeten worden, in een periode waarin het circadiane ritme slaap dicteert, dient men maatregelen te nemen om de alertheid te verhogen en zodoende het prestatieniveau op een hoog peil te houden. Het onderzoek is gericht op het bepalen van de bruikbaarheid en effectiviteit van middelen om de prestaties en inzetbaarheid van militairen tijdens militaire operaties te optimaliseren waarbij taakverrichting en fysieke aspecten centraal staan. Het onderzoek is uitdrukkelijk niet gericht op de mogelijkheid de militairen gedurende langere tijd wakker te houden.

Beschrijving van de werkzaamheden

In een eerder uitgevoerd onderzoek voor het Ministerie van Defensie is een selectie gemaakt van geschikte slaap- en alertheids-verhogende middelen (Busker *et al.*, TNO-rapport PML 2000-A2). In het hier gerapporteerde onderzoek zijn van de geselecteerde alertheidsverhogende middelen cafeine en modafinil de effecten op de inzetbaarheid tijdens slaapdeprivatie, op tijden dat normaal geslapen wordt, onderzocht in een relevant diermodel. Ook is de bruikbaarheid van flumazinil, een stof die de werking van slaapmiddelen tegengaat, onderzocht. Hiervoor is het slaapdeprivatiemodel in de marmosetaap ontwikkeld en gevalideerd (Philippens *et al.*, TNO rapport TNO-DV 2006 A270) waarna vervolgens de taakverrichting met behulp van een hand-oogcoördinatietaak en de fysieke aspecten met behulp van een locomotoractiviteitstest zijn onderzocht. Deze testen zijn verricht tijdens sessies in de late avond, de nacht en de vroege ochtend. Tijdens de sessies zijn de dieren wakker gehouden overeenkomend met een slaapdeprivatie van 24 uur.

Resultaten en conclusies

Beide stimulantia konden de vermoeidheidsaspecten veroorzaakt door slaapdeprivatie tegengaan. De met cafeïne behandelde dieren waren actiever dan de placebodieren gedurende de nachtsessies. De activiteit was vergelijkbaar met die van overdag. Cafeïne was niet in staat de fysieke vermoeidheidseffecten in de ochtendsessie tegen te gaan. Cafeïne verbeterde echter wel de taakverrichting gedurende alle testsessies. De effecten van langdurig gebruik van cafeïne op vermoeidheid en taakverrichting waren vergelijkbaar met eenmalig gebruik. De met modafinil behandelde dieren waren actiever dan de placebodieren gedurende alle testsessies. De activiteit was zelfs hoger dan de activiteit overdag. Modafinil verbeterde de taakverrichting tijdens de nachtsessies maar was niet in staat om dit effect tot aan de morgensessie vol te houden.
De positieve effecten op de activiteit waren ook terug te vinden na langdurig gebruik. De taakverrichting na langdurig gebruik is vergelijkbaar met het niveau van overdag gedurende alle sessies. Conclusies:

- Slaapdeprivatie leidt tot afname van activiteit en taakverrichting.
- Flumazinil is in staat om de werking van slaapmiddelen tegen te gaan.
- Cafeïne en modafinil zijn beide in staat de effecten van slaapdeprivatie op de

Slaap- en Alertheidsmanagement IV: Effect van de alertheidsverhogende middelen caffeïne en modafinil op taakverrichting in marmosets

vermoeidheid en taakverrichting uit te stellen of te voorkomen.
- Modafinil is effectiever in het stimuleren van de activiteit en cafeïne in het verbeteren van de taakverrichting.

Toepasbaarheid

Middelen om prestaties en alertheid op peil te houden mag en kan alleen ingezet worden voor zeer bijzondere omstandigheden wanneer de overleving van het individu of de groep op het spel staat. Onvoldoende rust kan vermoeidheid, chronisch slaapgebrek en verlies van alertheid tot gevolg hebben en kan tot een afnemend functioneren aanleiding geven. Dit onderzoek richt zich op het gebruik van medicamenten waarmee de prestaties en inzetbaarheid van militairen tijdens militaire operaties kunnen worden verbeterd en is uitdrukkelijk niet gericht op de mogelijkheid de militairen gedurende langere tijd wakker te houden.

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Samenvatting

Flumazinil met een selectieve affiniteit voor de benzodiazepine receptor waarop de slaapmiddelen ook binden, kan de verminderde taakverrichting na het gebruik van de slaapmiddelen temazepam, zolpidem en zaleplon herstellen tot het normale niveau van overdag. Dit impliceert dat flumazinil erg effectief kan zijn in een alertheid eisende situatie in het op peil houden van de normale prestaties kort nadat het personeel besloten heeft om te gaan slapen met behulp van een slaapmiddel. Echter, in geval men wakker moet worden uit slaap of men alert moet zijn op een tijdstip waarop het circadiane ritme voor slaap geprogrammeerd is, zal het gebruik van alertheids-verhogende middelen veel efficiënter zijn. Inderdaad blijkt uit deze studie dat slaapdeprivatie in de marmosetaap de prestatie en activiteit als gevolg van vermoeidheid sterk beïnvloedt, zoals ook het geval is in de mens.

De alertheidsverhogende stof cafeïne blijkt in staat te zijn om de door slaapdeprivatie veroorzaakte afname van de taakverrichting succesvol tegen te gaan en de activiteit tot bepaalde hoogte tegen te gaan. De gedeeltelijke compensatie door cafeïne van de door slaapdeprivatie geïnduceerde effecten komt overeen met de op peil blijvende alertheid en vigilantie na cafeïne gebruik geobserveerd in andere studies. De alertheids-verhogende stof modafinil blijkt ook in staat te zijn om de door slaapdeprivatie veroorzaakte afname van de prestaties tot bepaalde mate tegen te gaan en verhoogt zelfs de activiteit tot een hoger niveau dan de normale activiteit tijdens overdag.
Langdurig gebruik van cafeïne of modafinil heeft geen nadelig effect op de prestaties en de activiteit overdag en leidt tot vergelijkbare resultaten als na de eenmalige toediening tijdens een slaap gedepriveerde nacht. Langdurig gebruik van modafinil blijkt de afname van de prestaties door slaapdeprivatie heel goed tegen te gaan nadat er eerst in de late avond een afname van prestatie werd waargenomen. Eenmalige toediening van modafinil leidde tot een verbetering van de prestatie die gedurende de nacht afnam. Verder blijkt dat de activiteit, wat een maat is voor vermoeidheid, na de combinatie van het slaapmiddel temazepam en cafeïne of modafinil niet in die mate afgenomen te zijn zoals werd waargenomen na het slaapmiddel temazepam alleen, maar kwam overeen met de activiteit welke gemeten werd na cafeïne of modafinil alleen.

Dit betekent dat cafeïne en modafinil beiden effectief zijn in het tegen gaan van de afname van prestaties en vermoeidheid veroorzaakt door slaapdeprivatie. Tevens blijken de alertheidsverhogende middelen ook effectief te zijn in combinatie met een slaapmiddel en na langdurig gebruik niet tot nevenwerkingen op prestaties overdag te leiden. Modafinil bereikt zijn optimaal effect pas 2 tot 4 uur na orale toediening waardoor dit middel alleen gebruikt kan worden in situaties waarbij de missie van te voren is gepland. In situaties waarbij de inzet acuut en niet voorspelbaar is, zal modafinil niet geschikt zijn. Cafeïne, een snel en kortwerkend middel, zal daarentegen wel bruikbaar zijn voor korte scenario's. In geval een langdurig aanhoudende alertheid noodzakelijk is, zal een 'slow release' toediening nodig zijn.

Summary

Flumazinil with a selective affinity for the same receptor type as for the hypnotics (benzodiazepine receptor) is able to restore the normal daytime performance in a learned motor task which was previous decreased by the hypnotics temazepam, zolpidem and zaleplon. This indicates that in a military setting flumazenil might be very effective to maintain normal performance in case of an alertness demanding situation directly after personnel decided to facilitate their sleep by taking a hypnotic. However, in case personnel need to be waken from their spontaneous or drug induced sleep or they have to be alert during a time of the day that the circadian rhythm is programmed for sleep, the use of wake promoting drugs might be more efficient. Indeed, in this study it was shown that sleep deprivation in the marmoset monkey clearly affect the performance and the activity due to fatigue which is also found in human.

The alertness enhancer caffeine counteracted the sleep deprivation induced decline on the performance very well and on the activity to some degree. The partial counteraction of the sleep deprivation induced effects by caffeine also agrees with observations of maintained alertness and vigilance after caffeine observed in other studies.
The alertness enhancer modafinil counteracted the sleep deprivation induced decline on performance to some degree, and even improved the activity resulting in more activity compared to normal daytime activity.
Chronic use of caffeine or modafinil did not negatively affect the performance and the activity of the animals during daytime and resulted in comparable effects as what was found after a single use of these compounds during the sleep deprived night. Chronic use of modafinil counteracted the sleep deprivation induced decline during the night after showing a decline in the evening. When modafinil was given acutely the performance proceeded to decline from the evening measurement onwards.
Furthermore, the activity, reflecting the fatigue, after the combined use of the hypnotic temazepam and caffeine or modafinil was not reduced to that low level observed after temazepam alone but was comparable with the activity found after caffeine and modafinil alone.

This means that the stimulants caffeine and modafinil are both effective in reducing the sleep deprivation induced declines in performance. Moreover, the stimulants remain effective when used in combination with a sleep inducing drug and even after chronic use no worsening of day time performance was observed. Modafinil reach its maximum effect 2-4 hours after oral administration indicating that it can only be used in situation in which the operation is planned by forehand. In case unpredicted effort is needed in a short time, modafinil can not be used. Caffeine, a fast and short acting compound, should be useful for short scenarios. In case long term improved alertness is needed a slow release administration will be needed.

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1 Introduction

Regular and good quality sleep is vital for proper performance and a healthy life. Disturbed sleep is hazardous and can have multiple causes. In a military setting situations that induce disturbed sleep frequently occur. Round the clock activity requires rapid work shift changes and long night duties, which provoke sleep loss and high stress levels. This may result in excessive sleepiness. These situations have been documented in a separate TNO report [Simons and Valk, 1999]. Recommended possible solutions with direct usefulness in crew endurance plans included strategic napping, chronobiological treatments and the use of sleep-inducing and wake-promoting drugs.

Any pharmacological intervention may result in unwanted side-effects. Sleep drugs induce sleep, but may also cause undesired carry-over effects, such as excessive sleepiness after sleep when wakefulness is required by situational demands. For sleep and alertness maintenance this means that a combination of a short acting hypnotic drug and a fast acting stimulant drug may be necessary in some situations.

An overview of sleep-inducing and wake-promoting drugs to aid sleep and to enhance alertness during military service has been given in other TNO reports [Simons and Valk, 1999; Busker *et al.*, 2000]. The Busker *et al.* [2000] report includes a literature study on the use of animal models for human sleep-wake management, and a theoretical evaluation of potential candidate, e.g. hypnotics ('downers') for sleep induction and stimulants ('uppers') for wake maintenance.

To investigate effects of drugs, animal studies are in several respects preferable over human studies. Drug research on human volunteers has practical and ethical problems, and more invasive studies are not possible at all in humans. Therefore, for the current study the marmoset monkey model was used.

In order to select the optimal alertness enhancing drug for the management of sleep and wakefulness, the efficacy of such alertness enhancers in counteracting the effects of sleep deprivation on performance and activity need to be investigated. Therefore, the effects of caffeine and modafinil on behavioral performance were determined in the marmoset monkey during a night of sleep deprivation.

In a military setting it is very well possible that wakefulness needs to be promoted instantly in a conflict situation, even after having used a sleep-inducing drug. Therefore, in the current study the effects of flumazenil on counteracting the declines in performance after a hypnotic (temazepam, zolpidem or zaleplon) were investigated. But also the effects of the wake promoting drugs caffeine and modafinil, after the administration of the hypnotic temazepam, were measured on vigilance and activity of marmoset monkeys.

Because the selected wake promoting drugs are likely to be taken chronically in a military setting and should remain effective during that time, the efficacy of caffeine and modafinil after chronic use was also investigated.

2 Materials and methods

2.1 Animals

Primates are our closest animal relatives. Therefore, intuitively, it appears that the chance that a monkey will react in a similar way to drugs as we do is much greater than when a rodent or guinea pig is used. Indeed, neuro-anatomical studies show, for example, that there is much similarity of the regional distribution through the hippocampus of several neurotransmitter receptor types of marmosets and humans than of rats and humans [Kraemer *et al.*, 1995]. The marmoset has been shown to be a suitable model for man in OP toxicity studies [Van Helden *et al.*, 1983].

Seven adult male marmoset monkeys (*Callithrix jacchus; see Figure 1*), aged 4-6 years with initial body weights between 350-500 g were obtained from Harlan, United Kingdom. The monkeys were housed separately in cages (61 x 61 x 41 cm).
The ambient temperature in the housing room was regulated at 25 ± 2 °C and the relative humidity was maintained at > 60%. In this room a 12-hour day and night cycle was maintained. However, on the nights of sleep deprivation the light was kept on during the night. Daily they were fed with pellet chow, peanuts, fruit, boiled egg, baby biscuits, sunflower seeds, bread, beans, and fruit syrup after training or testing. Water was available *ad libitum*.
All aspects of animal care are described in Standard Operating Procedures, which are in agreement with current guidelines of the European Community. The independent TNO committee on Animal Care and Use approved all protocols for the animal experiments.

Figure 1 A picture of a marmoset monkey (*Callithrix jacchus*).

2.2 Drug administration

All compounds were administered orally. Temazepam (British Pharmacopoeia Chemical Reference Substance, Cat no. 455, Batch 2221), zolpidem and zaleplon were dissolved in fruit syrup (Karvan Cevitam) in a volume of 1 ml/kg. Modafinil (Modiodal: d,1-2-[(diphenylmethyl)sulfinyl]acetamide) was used in grinded tablet form (Laboratoire L. Lafon, France). One tablet contains 100 mg modafinil and filling compounds: lactose, cornstarch, magnesiummonosilicate $2H_2O$, sodiumcroscarmellose, polyvidon, talc and magnesium stearate. Before usage the grinded tablets were

homogenized freshly in a 10% sucrose solution in a volume of 2 ml/kg. Caffeine (Sigma Aldrich C8960) was dissolved in water in a volume of 1 ml/kg and prepared freshly before each administration.

In this study the efficacy of the alertness enhancers was tested based on the maximum blood levels of these compounds. Because of the fast absorption of caffeine in the blood compared to the absorption time of modafinil, caffeine was given shortly before the first test session and modafinil was given longer before the first test session [Philippens *et al.*, 2006: TNO-DV 2006 A268].

2.3 Study design

2.3.1 Hypnotics on daytime Hand Eye Coordination performance

During daytime period the animals were given a hypnotic (temazepam (15 mg/kg), zolpidem (3 mg/kg) or zaleplon (10 mg/kg)) or vehicle (fruit syrup) and were kept awake despite their drug induced drowsiness. The doses of the hypnotics were based on earlier studies in which the pharmacokinetic and sleep quality were studied. One hour after drug administration the HEC (HEC) performance was measured. Each animal received one hypnotic per test day and was allowed a washout period of 1 week before the next test day.
Subsequently, the antagonising effect of flumazenil (15 mg/kg) on the performance decline induced by hypnotics was tested on the HEC performance. Therefore, each animal was submitted to three other test days (one for each hypnotic) on which 30 min after the hypnotic the animals received flumazenil, and 30 min later their HEC performance was tested. Again there was a washout period of one week before the next test day.

2.3.2 Alertness enhancement during the night

The animals were kept awake during the night. On the test days the lights remained switched on during the dark period. Three times during the night the animals were tested on the HEC task, to test the vigilance performance, followed by the Bungalow test, to measure the physical capabilities. The evening tests started at 20:30 h, the night tests started at 1:00 h and the morning tests started at 6:30 h. On every test day and on every parameter the animals were tested in the same order.

To maintain a sustained level of the alertness enhancers during the night the compounds were administered more than once. Caffeine was administered three times: thirty minutes before each test (30, 5 and 10 mg/kg). Modafinil was administered twice: 3 hours before the evening tests (100 mg/kg) and 9 hours later (25 mg/kg). To measure the antagonising effects of the alertness enhancers on somnolence induced by sleep deprivation alone or the combination of sleep deprivation and the presence of a hypnotic, the hypnotic temazepam (15 mg/kg) was also administered more than once to maintain a sustained level of the hypnotic in the blood (one hour before each test). The vehicle compound (fruit syrup) was administered 4 hours before the start of the evening session. The dose and dosing schedules were the same when the caffeine and temazepam or modafinil and temazepam were tested together. The dose and timing of the administration were based on the peak activity of the used compounds [Philippens *et al.*, TNO-DV 2006 A268].

2.3.3 Alertness enhancement during the night after chronic administration

Modafinil (100 mg/kg, 2 h before lights off) and caffeine (30 mg/kg, 1 h before lights off) were administered daily for 14 days followed by a night as described in Section 2.3.2. During the chronic administration period the HEC and activity of the animals were tested in the afternoon before administration at day 4, 8 and 12.

2.4 Spontaneous exploratory behavior (Bungalow test)

The levels of activity and exploratory behavior play an important role in practically all measurements of animal behavior. A device called the 'Bungalow test' automatically and quantitatively assesses these parameters and is extensively described and validated [Wolthuis *et al.*, 1994; Philippens *et al.*, 2000]. The apparatus (see Figure 2) consists of four horizontally placed non-transparent boxes (23 x 23 x 23 cm) all interconnected by 6 PVC tubes (inner diameter 9.5 cm).

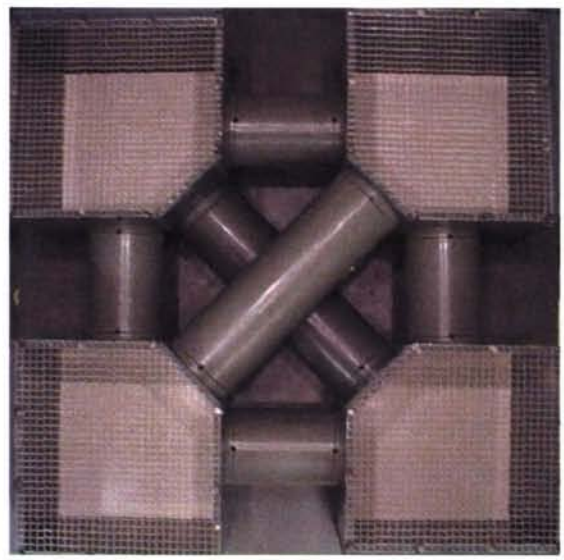

Figure 2 The setup of the bungalow task (view from above).

Each animal was placed in the same compartment at the start of each session.
The animals could freely move and change from one compartment to another during the 20-min session. A video tracking system (Ethovision, Noldus) registered the loco-motor activity of the animal, expressed as the number of compartment changes during the session.

2.5 Hand-eye coordination task

The hand-eye coordination (HEC) is a sensitive task for measuring controlled motor movements and vigilance. An automated robot-guided apparatus with positive reinforcement as a motivating stimulus (small pieces of marshmallow) has been used to asses the HEC [Philippens *et al.* 2000]. The marmoset is placed in front of a test panel provided with a window (8 x 5 cm). A robot arm presents a reward behind the window (see Figure 3).

For the test sessions during daytime (after the hypnotics) the task existed of 42 trials. Three trial types were executed, namely a non-moving reward in the middle of the window and two horizontally moving rewards at different speeds (0.04 and 0.08 m/s).

The animal was allowed one minute to grasp a non-moving reward. All trial types were presented 14 times.

For the test sessions during the night (after acute and chronic treatment) the task existed of 46 trials. Three trial types were executed, namely a non-moving reward in the middle of the window and two horizontally moving rewards at different speeds (0.04 and 0.08 m/s). The non-moving rewards were presented 14 times and the moving rewards 16 times in one session.

For the daytime test sessions during the chronic administration the task existed of 42 trials. These 42 trials existed of three trial types: one using a non-moving reward in the middle of the window and two horizontally moving rewards at different speeds (0.08 and 0.32 m/s). The higher speeds were used during daytime to investigate whether performance improved. Each type of trial was presented 14 times in one session.

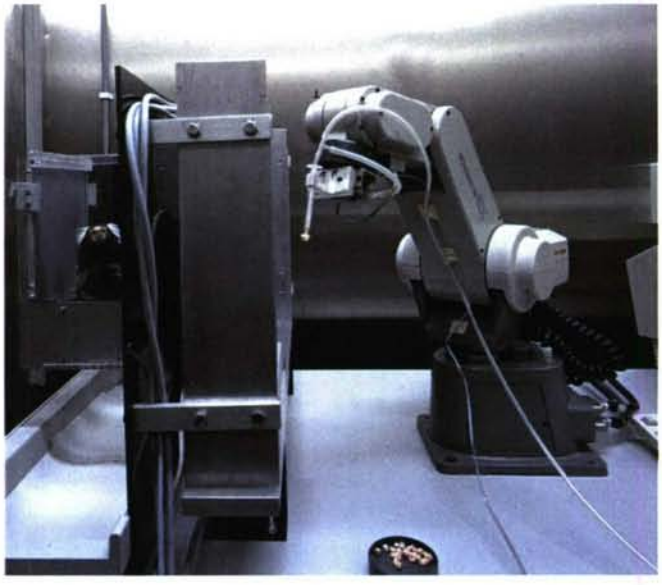

Figure 3 The setup of the hand-eye coordination (HEC) task.

At the beginning of each trial a sound signal was presented, intended to alert the animal. A pressure detector and infrared detectors in the window registered hits and attempts and speed of performance. A 'hit' was registered when the animal successfully retrieved the reward from the robot arm. The percentage of correct hits was used as a criterion to judge the performance of the animal. Before the start of the study, all animals were trained to collect at least 80% of the presented rewards.

2.6 Statistics

The data were statistically analysed using Repeated Measures ANOVA and paired t-test procedures in SPSS (SPSS inc, Chicago, USA). Differences were considered to be statistically significant if $P<0.05$.

3 Results

3.1 Daytime performance after hypnotics and counteraction by flumazenil

Figure 4 shows the average number of correct responses as percentage of performance after vehicle on the HEC task after the hypnotics temazepam, zolpidem and zaleplon and their combination with flumazenil.
Paired t-tests show that after temazepam ($P<0.05$), zolpidem ($P<0.05$) and zaleplon ($P<0.05$) the daytime HEC performance is decreased as compared to vehicle. Notably, when the hypnotics are followed by flumazenil treatment the performance is restored to normal levels, i.e. flumazenil effectively counteracts the hypnotic induced decline in HEC performance.

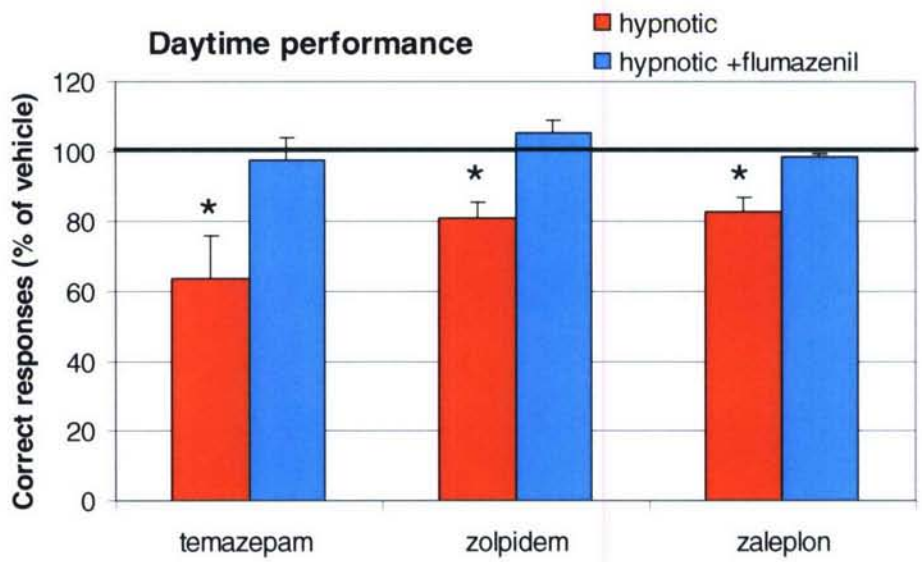

Figure 4 The average number of correct responses as percentage of performance after vehicle (+ SEM) on the HEC task. The effects of the hypnotics temazepam, zolpidem en zaleplon and their combination with flumazenil are shown. * indicate statistical significances compared to vehicle.

3.2 Performance on the HEC during sleep deprivation

3.2.1 Effects of caffeine (single use)

In Figure 5 the average number of correct responses on the HEC task after the caffeine treatment and the vehicle treatment are shown.
Repeated Measures ANOVA shows that there is a time dependent decrease in HEC performance after the vehicle treatment ($P=0.008$), which reflects the time-dependency of the effect of sleep deprivation on the HEC performance. Indeed, in the vehicle group the number of correct responses was less in the night ($P<0.05$) and morning ($P<0.05$) sessions as compared to baseline. No significant time-dependent effects were seen after caffeine treatment. This was emphasized by a trend towards a difference between

vehicle and caffeine treatment (P=0.097) on the night test session. Caffeine counteracts the sleep deprivation induced decline in HEC performance over time.

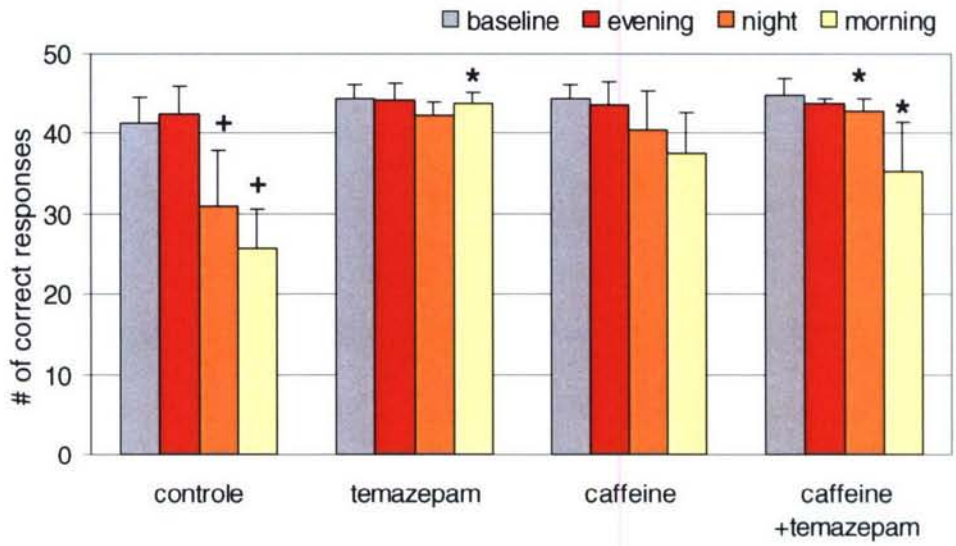

Figure 5 The average number of correct responses (+ SEM) on the HEC task for each of the test sessions after vehicle, temazepam, and caffeine treatment, and a combination of temazepam and caffeine. * indicate statistical significances compared to vehicle. + indicates statistical significance compared to baseline.

When analyzing the data of the HEC performance per speed (see Figure 6), it shows that the time dependent decline in HEC performance observed in the vehicle group is present for each individual speed (P<0.05). However, it also showed that despite a counteraction of the decline on an overall level by caffeine, the HEC performance was declined for the non-moving reward (speed 0; P<0.05).

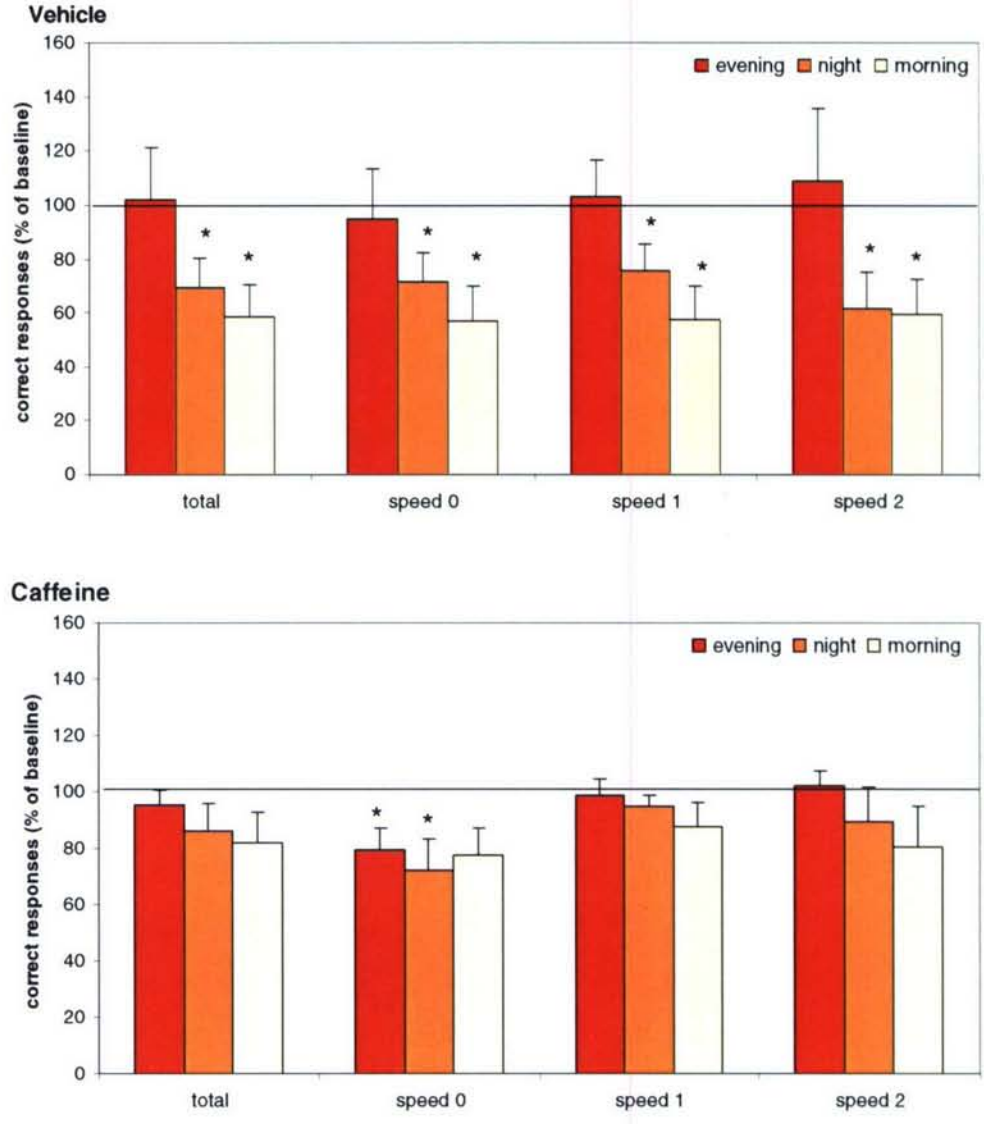

Figure 6 The average number of correct responses as a percentage of baseline (+ SEM) on the hand-eye coordination (HEC) task per speed for each of the test sessions after vehicle and caffeine. * indicate statistical significances compared to baseline. Speed 0= non moving reward, speed 1= 0.04 cm/s, speed 2= 0.08 cm/s.

3.2.2 *Effects of the combination of caffeine and temazepam (single use)*

Figure 5 shows the average number of correct responses on the HEC task after both the temazepam and the combination of temazepam and caffeine treatment, as well as after the vehicle treatment.

Repeated Measures ANOVA shows that there is a time dependent decrease in HEC performance after the vehicle treatment ($P=0.008$), which reflects the time-dependency of the effect of sleep deprivation on the HEC performance. Indeed, in the vehicle group the number of correct responses was less in the night ($P<0.05$) and morning ($P<0.05$) sessions as compared to baseline.

No significant time-dependent effects were seen after temazepam alone or the combination of temazepam with caffeine, i.e. the performance after the combination treatment was comparable to normal daytime performance (baseline).

This was emphasized by a significant difference (P<0.05) between vehicle and temazepam treatment and between the vehicle and the combination treatment on the morning test session.
These results indicate that treatment with a combination of temazepam and caffeine counteracts the sleep deprivation induced decline in HEC performance, as did the treatment with temazepam or caffeine alone.

3.2.3 *Effects of modafinil (single use)*

In Figure 7 the average number of correct responses on the HEC task after the modafinil treatment and the vehicle treatment are shown.
The time dependent decrease in HEC performance after the vehicle treatment (see Section 3.2.1) reflects the time-dependency of the effect of sleep deprivation on the HEC performance. After modafinil treatment a comparable significant time-dependent effect was observed (P=0.003). Further statistical analyses using paired t-tests shows that the HEC performance is significantly lower on the night test session (P<0.05) after modafinil treatment as compared to baseline. Thus, modafinil treatment does not completely counteract the sleep deprivation induced decline in HEC performance. However, during the night session performance seemed to be better after modafinil as compared to vehicle.

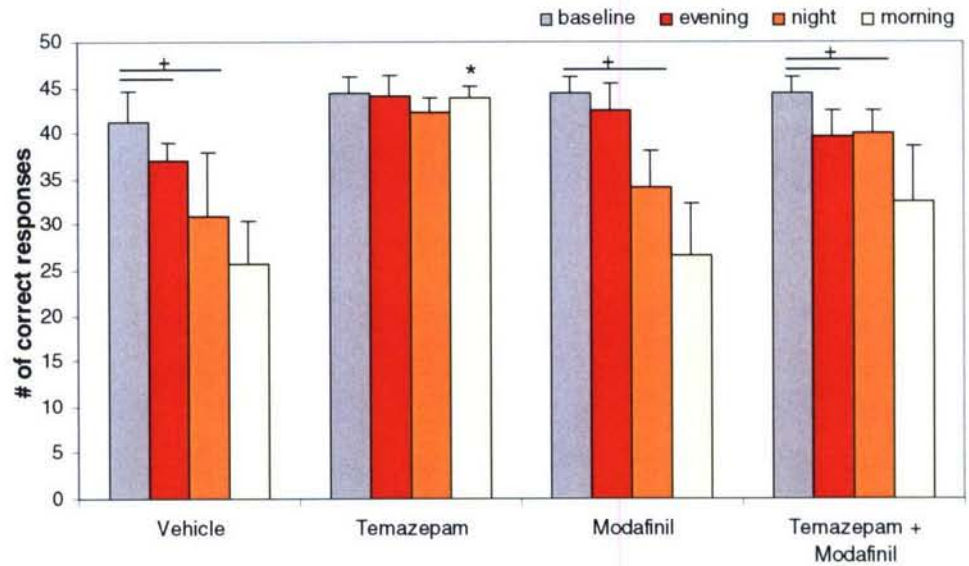

Figure 7 The average number of correct responses (+ SEM) on the HEC task for each of the test sessions after vehicle, temazepam, and modafinil treatment, and a combination of temazepam and modafinil. * indicate statistical significance compared to vehicle. + indicate statistical significances compared to baseline.

When analyzing the data of the HEC performance per speed (see Figure 8), it shows that the time dependent decline in HEC performance observed in the modafinil group is present per speed as well (P<0.05 or clear trends).

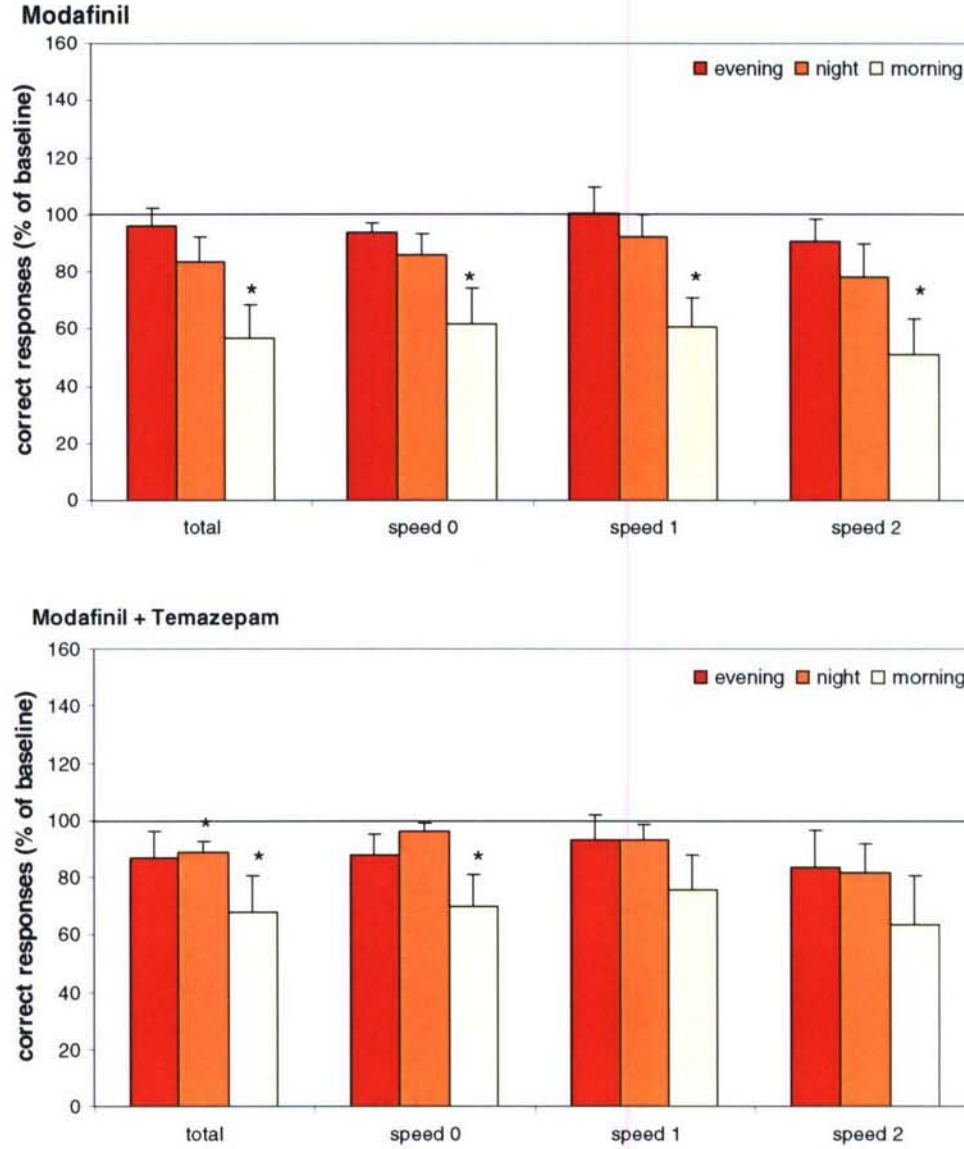

Figure 8 The average number of correct responses as a percentage of baseline (+ SEM) on the hand-eye coordination (HEC) task per speed for each of the test sessions after modafinil and after treatment with a combination of temazepam and modafinil. * indicate statistical significances compared to baseline. Speed 0= non moving reward, speed 1= 0.04 cm/s, speed 2= 0.08 cm/s.

3.2.4 *Effects of the combination of modafinil and temazepam (single use)*

Figure 7 shows the average number of correct responses on the HEC task after both the temazepam and the combination of temazepam and modafinil treatment, as well as after the vehicle treatment.

Repeated Measures ANOVA shows that there is a time dependent decrease in HEC performance after the treatment with a combination of temazepam and modafinil ($P=0.018$). Accordingly, significant differences between the baseline and the night ($P<0.05$) and morning test sessions ($P<0.05$) were observed after this combination treatment. When analyzing the data of the HEC performance per speed (see Figure 8), it shows that the time dependent decline in HEC performance observed in the combined temazepam and modafinil treatment group is present per speed as well ($P<0.05$ or clear trends). The results reflect that treatment with a combination of temazepam and

modafinil did not (fully) counteract the sleep deprivation induced effects on the HEC performance, as was the case for the treatment with modafinil alone. But there is still a tendency to an improvement compared to vehicle treatment.

3.3 Activity during sleep deprivation

3.3.1 *Effects of caffeine (single use)*

Figure 9 shows the average number of compartment changes in the bungalow test after both the temazepam and the caffeine treatment, as well as after the vehicle treatment. Repeated Measures ANOVA shows that there is a time dependent decrease in bungalow activity after the vehicle treatment ($P<0.001$), which reflects the time-dependency of the effect of sleep deprivation on the bungalow activity. Similar time-dependent effects were seen after temazepam ($P=0.035$) and caffeine ($P=0.01$) treatments. Further statistical analyses using paired t-tests shows that the bungalow activity is significantly lower on the night test session as compared to baseline after vehicle ($P<0.05$) and temazepam ($P<0.05$) treatments. Also, the bungalow activity is significantly lower on the morning test session as compared to baseline after vehicle ($P<0.05$), temazepam ($P<0.05$) and caffeine ($P<0.05$) treatments.

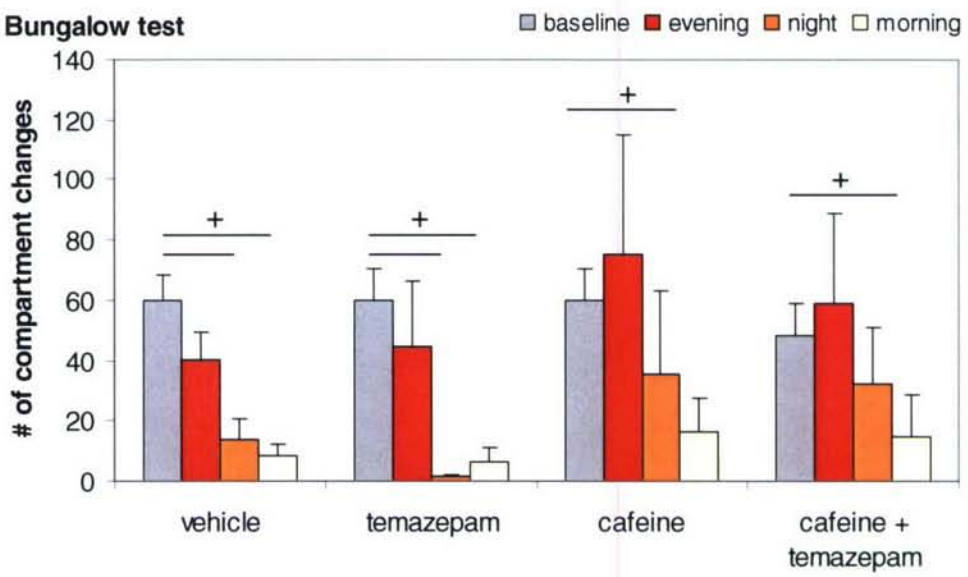

Figure 9 The average number of compartment changes (+ SEM) on the bungalow test for each of the test sessions after vehicle, temazepam and caffeine treatment, as well as after treatment with a combination of temazepam and caffeine. + indicate statistical significance compared to baseline.

3.3.2 *Effects of the combination of caffeine and temazepam (single use)*

Figure 9 also shows the average number of compartment changes in the bungalow test after the treatment with a combination of temazepam and caffeine.
Repeated Measures ANOVA shows that there is a time dependent decrease in bungalow activity after the treatment with a combination of temazepam and caffeine ($P=0.019$). Accordingly, a significant difference between the baseline and the morning session was observed after this combination treatment ($P<0.05$). The results reflect that treatment with a combination of temazepam and caffeine did not completely counteract the sleep

deprivation induced effects on the bungalow activity, as was the case for the treatment with temazepam or caffeine alone. However, during the night session performance seemed to be somewhat better after temazepam or the combination of temazepam and caffeine as compared to vehicle.

3.3.3 *Effects of modafinil (single use)*

Figure 10 shows the average number of compartment changes in the bungalow test after both the temazepam and the modafinil treatment, as well as after the vehicle treatment. The time dependent decrease in bungalow activity after the vehicle treatment (see Section 3.3.1) reflects the time-dependency of the effect of sleep deprivation on the bungalow activity. Repeated Measures ANOVA shows that there is a time dependent change in bungalow activity after the modafinil treatment (P=0.032). Initially (evening) there is a trend towards an increased bungalow activity (baseline vs evening: P=0.06) which is followed by a tendency to return to baseline levels (evening vs morning: P=0.051). Further statistical analyses using paired t-tests shows that the bungalow activity is significantly higher after modafinil treatment compared to vehicle, for both the evening (P<0.05) and the night test session (P<0.05).

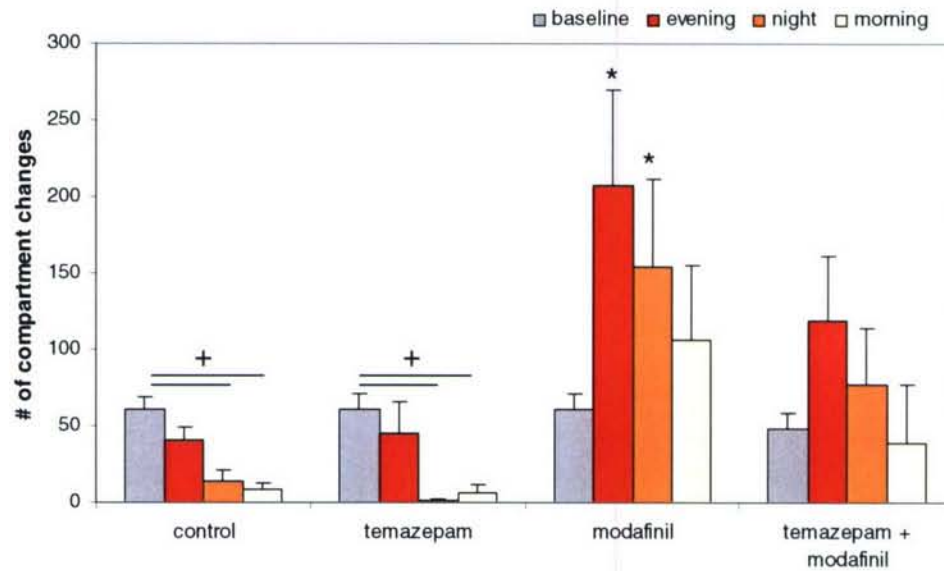

Figure 10 The average number of compartment changes (+ SEM) on the bungalow test for each of the test sessions after vehicle, temazepam and modafinil treatment, as well as after treatment with a combination of temazepam and modafinil. + indicate statistical significance compared to baseline. * indicate statistical significance compared to vehicle.

3.3.4 *Effects of the combination of modafinil and temazepam (single use)*

Figure 10 also shows the average number of compartment changes in the bungalow test after the treatment with a combination of temazepam and modafinil.
There was no significant time-dependent effect on the bungalow activity of treatment with a combination of temazepam and modafinil. These results indicate that treatment with a combination of temazepam and modafinil counteracts the sleep deprivation induced decline in bungalow activity.

3.4 Effects of chronic use of caffeine and modafinil during sleep deprivation

3.4.1 Daytime performance and activity

The data for the daily test sessions and the nightly test session for the HEC task are analysed separately since there were differences in target movement speed between the daily and nightly test sessions (see Section 2.5).

Figure 11 shows the correct responses as a percentage of baselines on the HEC task for three daily test sessions after chronic treatment with caffeine or modafinil.
Repeated Measures ANOVA shows that there is no effect of chronic caffeine or modafinil treatment on HEC performance as measured on three daily test sessions. Also, no significant differences between caffeine and modafinil were observed on any of the three daily test sessions for any speed.

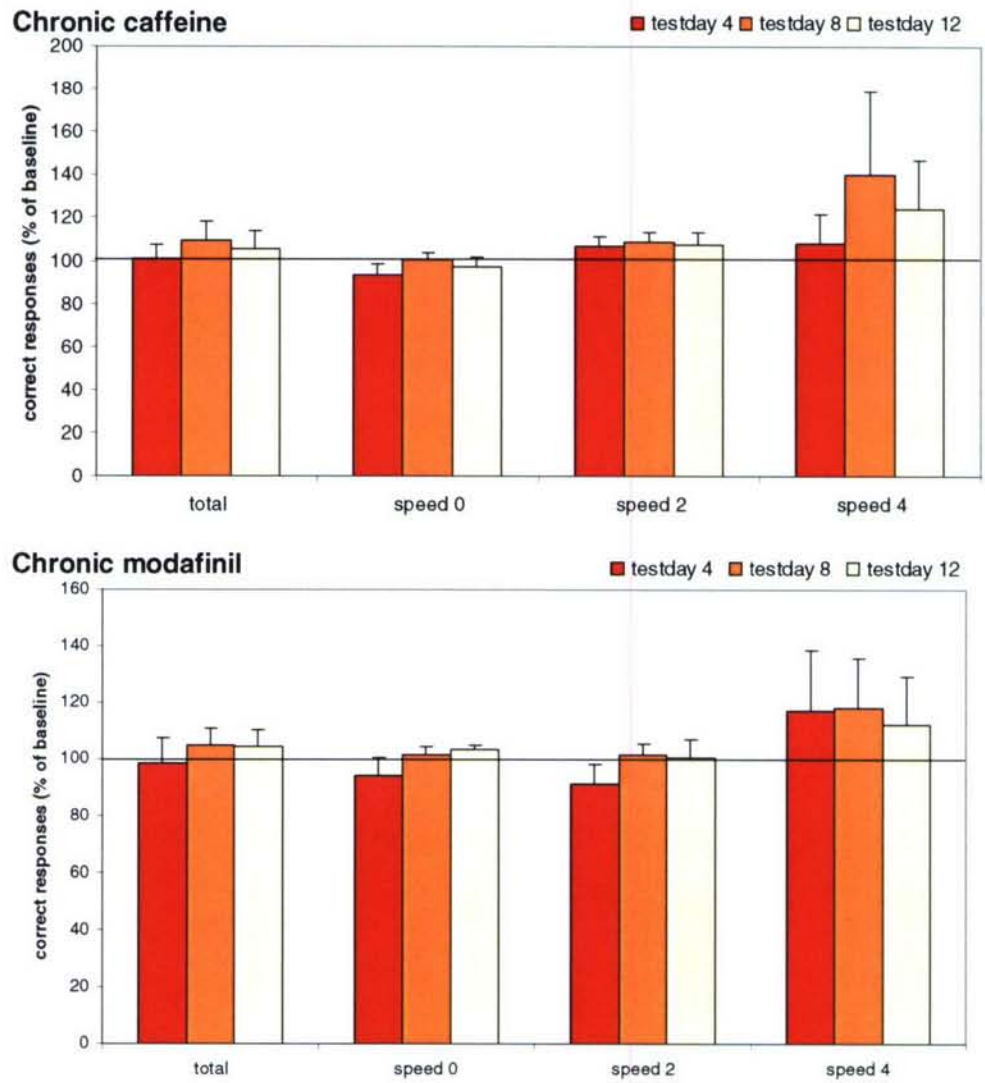

Figure 11 The correct responses as a percentage of baseline (+ SEM) on the hand-eye coordination (HEC) task, per speed, for three daily test sessions (testday 4= before 4th administration, testday 8= before 8th administration, testday 12= before 12th administration) after chronic treatment with caffeine (upper panel) or modainil (lower panel). Speed 0= non moving reward, speed 1= 0.08 cm/s, speed 2= 0.32 cm/s.

Figure 12 shows the compartment changes as a percentage of baselines on the bungalow test for three daily test sessions during the period of chronic administration (t=4, 8, and 12d). Repeated Measures ANOVA shows that there is no effect of chronic caffeine or modafinil treatment on bungalow activity as measured on three daily test sessions. Also, no significant differences between caffeine and modafinil were observed.

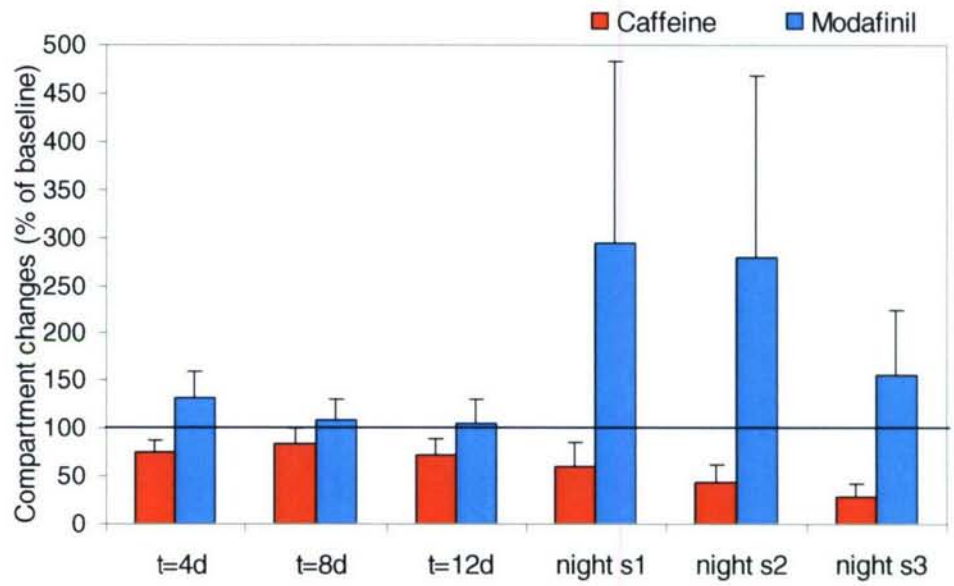

Figure 12 The compartment changes as a percentage of baseline (+ SEM) on the bungalow test for three daily test sessions (4d= before 4th administration, 8d= before 8th administration, 12d= before 12th administration) during the period of chronic administration and the three night test sessions (s1=evening, s2=night, s3=morning) after 14 days of chronic treatment with caffeine or modafinil.

3.4.2 *Nighttime performance and activity*

Figure 12 shows the compartment changes as a percentage of baselines on the bungalow test for the three night test sessions after 14 days of chronic treatment with caffeine or modafinil. Repeated Measures ANOVA shows that after 14 days of chronic caffeine treatment there was time-dependent decline in bungalow activity during the nightly test sessions (P=0.015), such a significant decline was not observed after 14 days of chronic modafinil treatment. However, no significant differences between caffeine and modafinil were observed on any of the three nightly test sessions.

Figure 13 shows the correct responses as a percentage of baselines on the HEC task for the three nightly test sessions after 14 days of chronic treatment with caffeine or modafinil. Repeated Measures ANOVA shows that there is no effect of 14 days of either chronic caffeine or modafinil treatment on HEC performance as measured on the three nightly test sessions (total of speeds). However, after modafinil there is a clear tendency towards a decline in performance during the evening session which returns towards baseline in later sessions. This is supported by a significant decrease in performance on the non-moving trials (speed 0) during the evening session (P<0.05). After caffeine a trend towards overall declined performance was observed, albeit less clear than after modafinil. Compared with vehicle treatment both compounds are able to prevent the decline in performance induced by sleep deprivation.

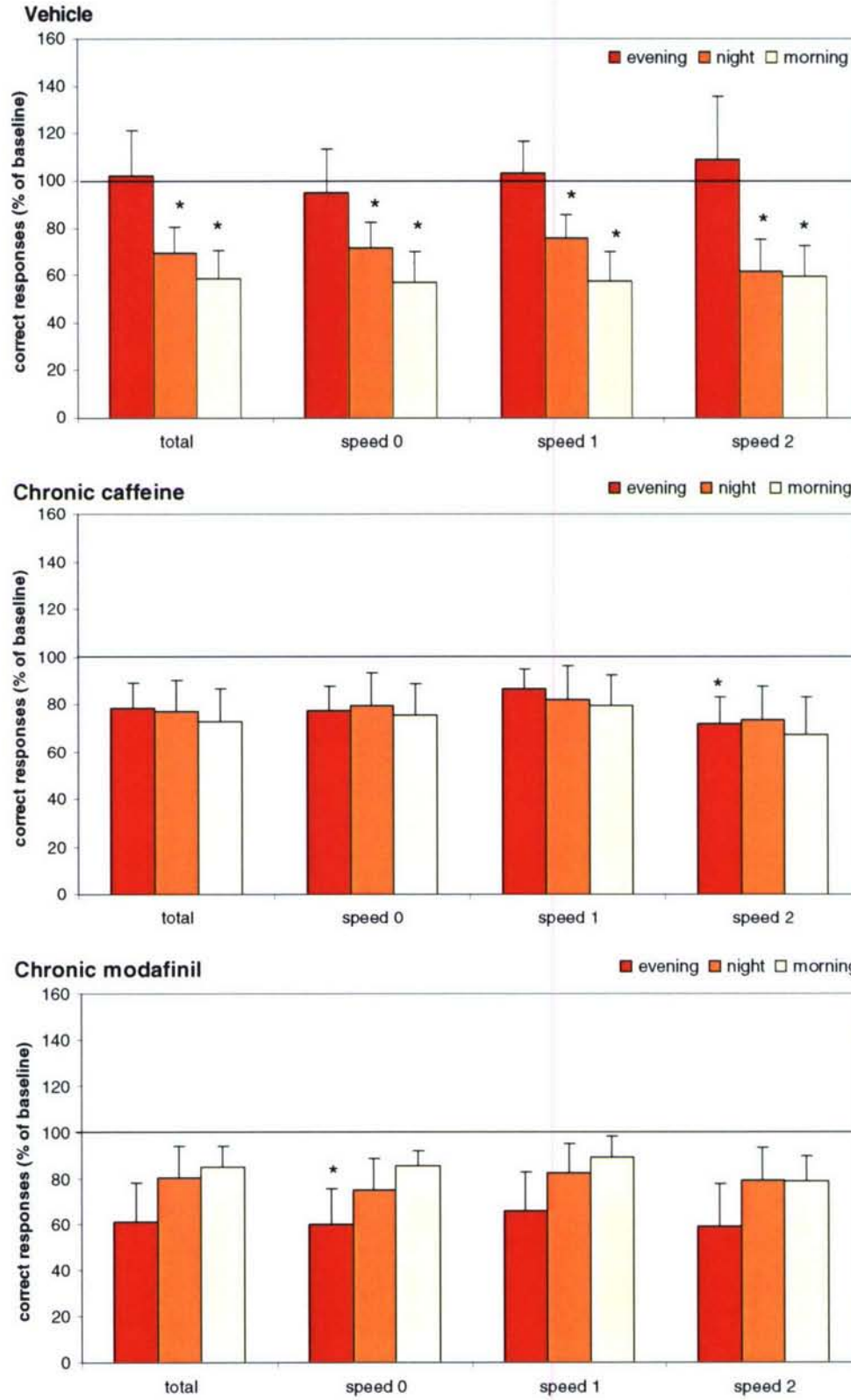

Figure 13 The correct responses as a percentage of baseline (+ SEM) on the hand-eye coordination (HEC) task for the three night test sessions after 14 days of vehicle treatment (upper panel) and chronic treatment with caffeine (middle panel) or modafinil (lower panel). * indicate statistical significance compared to baseline. Speed 0= non moving reward, speed 1= 0.04 cm/s, speed 2= 0.08 cm/s.

4 Discussion

4.1 Performance after hypnotics

The results show that after the hypnotics temazepam, zolpidem and zaleplon the daytime performance on the HEC task declined. However, when flumazenil was administered after having received a hypnotic the performance was restored to normal levels. These results indicate that in a military setting flumazenil might be very effective for the maintenance of normal performance in case of an alertness demanding situation *directly* after personnel decided to facilitate their sleep by taking a hypnotic. Of course, in most cases personnel need to be waken from their sleep (spontaneous or drug induced) in order to respond to the alertness demanding situation. In case this situation occurs during a time of the day that the circadian rhythm is programmed for sleep the use of wake promoting drugs might be more efficient (see Section 4.3).

4.2 Validation of sleep deprivation effects

The results of the vehicle group show that during sleep deprivation the performance on the HEC task as well as the activity in the bungalow task decreases over night. Accordingly, sleep deprivation effects on performance have been observed in other species and humans [Rogers *et al.*, 2003; Silva *et al.*, 2004; Porrino *et al.*, 2005; Blatter *et al.*, 2006]. The replication of these sleep deprivation effects in this study shows that the marmoset monkey can be considered to be a valid animal model for sleep deprivation.

4.3 Effects of wake promoting drugs after single use

4.3.1 Caffeine

Caffeine counteracted the sleep deprivation induced decline on the HEC performance very well and on the activity on the bungalow task to some degree. Accordingly, caffeine has been shown to counteract the decline in response speed, a factor in HEC performance, observed after sleep deprivation [Penetar *et al.*, 1994; Tharion *et al.*, 2003; Tikuisis *et al.*, 2004; McLellan *et al.*, 2005a]. The partial counteraction of the sleep deprivation induced effects by caffeine in the present study also agrees with observations of maintained alertness and vigilance after caffeine observed in other studies [McLellan *et al.*, 2005b; Kamimori *et al.*, 2005].
Interestingly, despite some counteraction of the sleep deprivation effects, the sleep deprivation induced decline is clearly present for non-moving trials on the HEC task (see Figure 5). This might indicate that the salience of the target (moving targets being more salient) plays a role in the level of counteraction of the sleep deprivation effect by caffeine, i.e. attention factors mediate the caffeine effect on HEC performance.

4.3.2 Modafinil

Modafinil counteracted the sleep deprivation induced decline on the HEC performance to some degree. In contrast to the effect of caffeine, the HEC performance after modafinil was independent of the movement speed of the target.
On the activity in the bungalow test, modafinil did not only counteract the sleep deprivation induced decline but resulted in more activity than during baseline, i.e.

hyperactivity. Similar effects of modafinil on activity have been observed in an earlier study in marmoset monkeys at our laboratory [Van Vliet *et al.*, 2006] as well as in other species [Duteil *et al.*, 1990; Hermant *et al.*, 1991; Simon *et al.*, 1994; Simon *et al.*, 1996]. Such an increase in activity is not reported in humans, however related side effects such as nervousness and insomnia have been observed [Robertson and Hellriegel, 2003].

4.4 Combined use of temazepam and a stimulant

4.4.1 Temazepam

Temazepam did not affect the sleep deprivation induced decline in locomotor activity in the bungalow task. It was not surprising, based on the use of temazepam as an hypnotic [Paul *et al.*, 2004; Caldwell *et al.*, 2003], that temazepam facilitates the drowsiness that was already induced by the sleep deprivation.
In contrast, temazepam did counteract the sleep deprivation induced decline in HEC performance. Possibly, the animals were triggered out of their drowsy state, by the sounds of the movements of the robot arm, long enough to perform the HEC task in a normal manner. Perhaps, the animals even had temazepam induced micro-naps between the trials on the HEC task which might have facilitated a good HEC performance.
The lack of such a counteraction of sleep deprivation induced declines in psychomotor performance in human studies might be explained by the fact that humans will try to cooperate with the task, i.e. force themselves to be as alert as possible and therefore are unlikely to have micro-naps. Furthermore, the difference with this present study was that temazepam was given repeatedly during the night. In al other reported studies temazepam was given only once in the beginning of the night. In our former experiment [Philippens *et al.*, 2006: TNO-DV 2006 A270] temazepam was also administered only once before the start of the night and the animals were allowed to have a short nap. In that case temazepam did show a decline on the already decreased performance level which is also found in other studies. It is a remarkable finding that sustained levels of temazepam leading to clear sleepiness, reflected in the low activity, improved the performance. An increase of performance which was mainly due to the increase of the small moving trials and not of the less notable non-moving trials.
It is important to emphasize that temazepam is not a stimulant and, despite its positive effect on psychomotor performance after sleep deprivation, it can not be used in a real-life setting for the counteraction of sleep deprivation induced declines in performance. Obviously, the somnolent effects of temazepam are truly unwanted when personnel needs to be alert and perform, even when they are sleep deprived.

4.4.2 Temazepam combined with a stimulant

The activity in the bungalow after the combined use of temazepam and either stimulant did not show the large reduction in activity which was observed after temazepam alone. In general, the effects that were observed after the stimulants caffeine and modafinil alone were also observed when these stimulants were administered when temazepam was given as well. This is probably due to the counteraction of the somnolence effect of temazepam by the stimulants as was observed in the bungalow task. Notably, the remarkable positive effect of temazepam alone on the HEC performance was diminished by modafinil and to a certain degree by caffeine as well.

4.5 Effects after long term use

4.5.1 *Caffeine*

As caffeine is used on a daily basis, the wake-promoting efficiency of caffeine in habitual users could be diminished. Therefore the effects between no previous caffeine use and long term use were compared. During the daytime sessions of the chronic treatment period, caffeine did not seem to affect the HEC performance or bungalow activity of the animals.

During the sleep deprived night with caffeine, there appears to be a non-significant decline of HEC performance compared to baseline, i.e. chronic caffeine counteracted the sleep deprivation induced decline during the night to some degree. Interestingly, after acute caffeine treatment the HEC performance was mostly impaired on the non-moving trials whereas after chronic treatment no such selectivity in impairing HEC performance was observed. This can be the result of arousal effects of caffeine. Increase in arousal improves performance on a task where relatively few sources of information have to be monitored, particularly under conditions when the need for selective attention is stressed by time pressure [Fredholm *et al.* 1999]. The preference for rewards at a certain speed of the HEC task seems to be only sensitive in the first hours after acute caffeine use. During the morning sessions of the acute treatment the effects were more equal without changes in the total score and the preference was absent in the chronic caffeine treated animals. Probably the level of arousal induced by this treatment is different due to tolerance to caffeine and therefore the preference for fast moving rewards is not apparent.

On the bungalow task no clear difference was observed between the effects of the acute and chronic caffeine treatments, although both treatment protocols were not able to counteract the time-dependent increase in fatigue. Chronically treated animals developed some tolerance for caffeine reflected in a tendency towards a lower activity in the evening than that of the acutely treated animals, although this was not observed after the night and morning sessions.

4.5.2 *Modafinil*

During the daytime sessions of the chronic treatment period, modafinil did not seem to affect the HEC performance or bungalow activity of the animals.

During the sleep deprivation period modafinil seems to be very successful to prevent fatigue as the activity was clearly higher or comparable to daytime values during all sessions. The effect of modafinil on the bungalow activity which was observed after acute treatment can still be observed albeit to a lower degree. Modafinil is known to increase activity in rodents and naïve marmosets [van Vliet *et al.* 2006; Simon *et al.* 1995; Ward *et al.* 2004], which is reflected in restlessness in humans [Randal *et al.* 2003]. On the HEC after chronic modafinil treatment, there appears to be a decline of the performance during the evening session compared to baseline which returns to baseline later on the night. Chronic use of modafinil counteracted the sleep deprivation induced decline during the night after showing a decline in the evening. The shift in effect of chronic modafinil on the HEC can be due to tolerance to the compound, although this is not reported in humans [Lyons *et al.* 1991; Mitler *et al.* 2000]. When modafinil was given acutely (see Section 3.2.3) the performance proceeded to decline from the evening measurement onwards. These effects on the HEC task refute the possible tolerance to modafinil as chronic treatment prevented the decline in vigilance in the morning sessions of the acute modafinil treatment. Therefore it can be concluded that modafinil does not induce tolerance.

4.6 Application of stimulants in a military setting

Besides the findings in this study other reports and papers emphasizes the usefulness of stimulants in sustained operations.
Modafinil did not affect the recovery sleep which was similar to placebo. Moreover, the length of the recovery sleep was shorter after modafinil suggesting that the need for recovery sleep was less than after placebo [reviewed in Buguet *et al.*, 2003]. Also caffeine is unlikely to have major disruptive effects on the sleep that follows 8 hours or longer after administration [Bonnet *et al.*, 2005].
Modafinil is classified as a Schedule IV drug under the American controlled substances act. However, for the use of modafinil medical prescription is needed.
As a stimulant, caffeine, because of its nonprescription status, is in a unique class that gives it significant benefits such as easy access, extensive research findings, and broad familiarity with effects. However, a liability is that caffeine use is already widely used in society (coffee and other caffeine containing beverages and foods) that individuals can develop some degree of tolerance [Bonnet *et al.*, 2005].
Also, evidence for moderate abuse liability and the development of moderate physical dependence has been shown for caffeine [Bonnet *et al.*, 2005], which might interfere with caffeine's application for prolonged use. There is limited evidence concerning the abuse potential for modafinil because of its relatively recent availability. However, so far studies of modafinil have not shown a pattern of adverse effects similar to those of drug abuse [Bonnet *et al.*, 2005]. In all, modafinil seems to be a candidate for use of sleep-wakefulness management in a military setting. However, in humans modafinil was shown to have a disruptive effect on self-monitoring, inducing a reliable 'overconfidence' effect, i.e. an overestimation of actual performance, which was particularly marked 2-4 h post-dose [Baranski and Pigeau, 1997]. Such an overconfidence effect is undesirable in a military setting.
Concerning the requisition for the short scenarios in which rapid changes from daytime missions to nighttime missions and vica versa will take place, a fast acting drug will be needed. The pharmacokinetics of modafinil indicates that this stimulant can only be used in situation in which the operation is planned by forehand. Modafinil reach its maximum 2-4 hours after oral administration. In case unpredicted effort is needed in a short time, modafinil can not be used.
The pharmacokinetics of caffeine indicates that this stimulant should be useful for short scenarios. It is a fast and short acting compound. In case long term improved alertness is needed a slow release administration will be needed.

5 Conclusion

As all drugs may produce side-effects, consideration for usage should be based on necessity and for a minimal amount of time. Flumazenil can be effective for the maintenance of normal performance in case of an alertness demanding situation *directly* after personnel decided to facilitate their sleep by taking a hypnotic. Of course, in most cases personnel need to be waken from their sleep (spontaneous or drug induced) in order to respond to the alertness demanding situation. In that case the use of wake promoting drugs might be more efficient. The stimulants caffeine and modafinil are both effective in reducing the sleep deprivation induced declines in performance. Moreover, the stimulants remain effective when used in combination with a sleep inducing drug and even after chronic use no worsening of day time performance was observed. Thus if soldiers are not allowed to sleep in specific situations, then the use of caffeine or modafinil is an effective countermeasure strategy to ensure the operational efficacy, even after having taken a hypnotic. Because of the fast absorption of caffeine in the blood compared to the absorption time of modafinil, caffeine would be favorable as an alertness enhancer in short scenarios.

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7 Signature

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15. ABSTRACT (MAXIMUM 200 WORDS (1044 BYTE))

Flumazenil might be effective to maintain normal performance in case of an alertness demanding situation directly after taking a hypnotic. However, in case personnel have to be alert during a time of the day that the circadian rhythm is programmed for sleep, the use of wake promoting drugs might be more efficient.
The alertness enhancer caffeine counteracted the sleep deprivation induced decline on the performance and activity. Modafinil even improved the activity. Chronic use of caffeine or modafinil did not negatively affect the performance and the activity during daytime and resulted in comparable effects as after a single use of these compounds.
This means that caffeine and modafinil are both effective in reducing the sleep deprivation induced declines in performance. Moreover, the stimulants remain effective when used in combination with a hypnotic and even after chronic use no worsening of day time performance was observed. Modafinil reach its maximum effect 2-4 hours after oral administration indicating that it can only be used in situation in which the operation is planned by forehand. Caffeine, a fast and short acting compound, should be useful for short scenarios. In case long term improved alertness is needed a slow release administration will be needed.

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